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EXAMINER
BERTOGLIO, VALARIE E

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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/605,415	MACRAE ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-12,14,15,17-24,27,28,30,31,33-36,40-45,47-50,52-55,57,58,60,71-83* is/are pending in the application.

4a) Of the above claim(s) *73-82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-12,14,15,17-24,27,28,30,31,33-36,40-45,47-50,52-55,57,58,60 and 83* is/are rejected.

7)☒ Claim(s) *71,72* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's reply dated 10/25/2007 has been received: Claims 1,4,20,36,40,42,49,52, and 58 are amended. Claims 71-83 are added. Claims 6-7,13,16,25-26,29,32,37-39,46,51,56,59 and 61-70 are cancelled.

Election/Restrictions

The restriction requirement was not made final in the previous office action dated 04/25/2007. Applicant continues to traverse the restriction requirement dated 10/10/2006. Applicant traverse the restriction on the grounds that the claimed method can be used with any zebrafish, which would include mutant, transgenic, and wild-type (non-transgenic). However, it is maintained that the state of the art at the time of filing brought about different considerations in terms of enablement and obviousness or anticipation with respect to use of transgenics and mutants. The basis of the restriction is set forth at pages 3-4 of the restriction requirement dated 10/10/2006. For example, use of the claimed method with a transgenic fish would require use of transgenic technology as well as a search of such literature involving heart specific promoters in zebrafish. These considerations are not necessary for use of wildtype fish. Applicant expresses concern that claims 1,4,20,40,42 and 52 will not be examined for its full breadth as the claims are divided, and that the claimed method can be used on any fish. To the extent claims 1,4,20,40,42 and 52 fail to require use of any mutation or transgene, the claims are examined for their full breadth. However, any methods dependent from such claims that require making a mutant or transgenic or analysis using a mutation or transgene is considered outside the scope of the elected invention. The requirement is still deemed proper and is therefore made FINAL.

Applicant has added claims 71-83. Claims 71 and 72 are objected to as set forth below. Newly submitted claims 73-82 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 73 is drawn to a nucleic acid that is not part of the

elected invention. Claims 74-82 are drawn to transgenic zebrafish or to those otherwise comprising an exogenous nucleic acid, which is not encompassed by the elected invention.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 73-82 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1-5,8-12,14,15,17-24,27-28,30-31,33-36,40-45,47-50,52-55,57-58,60,71,72 and 84 are under consideration.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 16,32,36 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1) The rejection of claims 1-3,9-12,14-21,23,27-28,30-35,40,43-45,47,48,52-55,57 and 60 under 35 U.S.C. 102(e) as being anticipated by Zon (**US2005/0155087**; EFD 12/17/2001) as evidenced by Serbedzija (**US 6,656,449**) is withdrawn in light of Applicant's amendments to the claims requiring computer-automated analysis in the method.

2) The rejection of claims 1-3,5,9-12,14-21,23-24,27-28,30-35,40,43-45,47,48,52-55,57 and 60 under 35 U.S.C. 102(e) as being anticipated by Serbedzija (US 6,656,449, filed 09/23/2000) is withdrawn in light of Applicant's amendments to the claims requiring computer-automated analysis in the method. While Serbedzija did teach use of computers to automate analysis, recording and analysis of a recording was not taught.

3) The rejection of claims 1-3,9-10,12,14-18,20-21,23,27-28,30,32-35,40,43-45,47,48,52-55,57 and 60 under 35 U.S.C. 102(b) as being anticipated by Peterson et al. [**PNAS**, 97:12965-12969, 2000] as evidenced by Serbedzija (US 6,656,449) is withdrawn in light of Applicant's amendments to the claims requiring computer-automated analysis in the method..

4) The rejection of claims 1-3,5,8-9,11-12,14-21,22-24,27,30-35,40,43-45,47,48,52-55,57 and 60 under 35 U.S.C. 102(a) and (e) as being anticipated by Artemis pharmaceuticals Inc., (WO 01/92874, filed

05/19/2001, published 12/06/2001), is withdrawn in light of Applicant's amendments to the claims requiring computer-automated analysis in the method..

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) The rejection of claims 4,36,37,41,42,49,50 and 58 under 35 U.S.C. 103(a) as being unpatentable over Zon (US2005/0155087; EFD 12/17/2001) as evidenced by Serbedzija (US 6,656,449) as applied to claims 1-3,9-12,14-21,23,27-28,30-35,40,43-45,47,48,52-55,57 and 60 above, and further in view of Camm (2000, IDS) is withdrawn in light of Applicant's amendments to the claims requiring computer-automated analysis in the method.

2) The rejection of claims 4,36,37, 41,42,49,50 and 58 under 35 U.S.C. 103(a) as being unpatentable over Serbedzija (US 6,656,449, filed 09/23/2000) as applied to claims 1-3,5,9-12,14-21,23-24,27-28,30-35,40,43-45,47,48,52-55,57 and 60 above, and further in view of Camm (2000, IDS) is withdrawn in light of Applicant's amendments to the claims requiring computer-automated analysis in the method.

3) The rejection of claims 4,36,37, 41,42,49,50 and 58 under 35 U.S.C. 103(a) as being unpatentable over Peterson et al. [PNAS, 97:12965-12969, 2000] as evidenced by Serbedzija (US 6,656,449) as applied to claims 1-3,9-10,12,14-18,20-21,23,27-28,30,32-35,40,43-45,47,48,52-55,57 and 60 above, and further in view of Camm (2000, IDS) is withdrawn in light of Applicant's amendments to the claims requiring computer-automated analysis in the method.

4) The rejection of claims 4,36,37, 41,42,49,50 and 58 under 35 U.S.C. 103(a) as being unpatentable over Artemis pharmaceuticals Inc., (WO 01/92874, filed 05/19/2001, published 12/06/2001), as evidenced by Serbedzija (US 6,656,449) as applied to claims 1-3,5,8-9,11-12,14-21,22-24,27,30-35,40,43-45,47,48,52-55,57 and 60 above, and further in view of Camm (2000, IDS) is withdrawn in light of Applicant's amendments to the claims requiring computer-automated analysis in the method.

The following new rejections are necessitated by claim amendment.

1) Claims 1-3,5,9-12,14,15,17-21,23-24,27-28,30-36,40,43-45,47,48,52-55,57 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Serbedzija (US 6,656,449, filed 09/23/2000) taken with Franciosi *et al* (2000, Teratology, 62:189-194).

Serbedzija taught a method of evaluating a test agent comprising method steps of contacting a zebrafish with a test agent, and evaluating a parameter of heart function (claim 1). Serbedzija taught screening compounds from the NCI Open Synthetic Compound Collection library (col. 23, lines 7-14) by administering the compounds in 6-96 well assay array plates to wildtype zebrafish embryos (col. 23, lines 35-40). Parameters to be evaluated included heart rate (col. 23, lines 54-55). Serbedzija teaches that the test compound can be a small molecule, nucleic acid or a protein (col. 14, lines 19-43) and that combinatorial libraries of compounds can be used. Serbedzija teaches screening multiple compounds in parallel using a multi-well plate. Serbedizija also taught that larval stages can be used in the method (col. 12, lines 46-47). Serbedzija also teaches permeabilizing the zebrafish by administering the agents in a DMSO solution (col. 20, lines 53-58).

Serbedzija taught computer-based screening automation as claimed, but did not teach recording the heart and analyzing the recording.

However, Franciosi taught computer-based screening automation by image recording of the heart of chick embryos using a microscope coupled to a Metamorph Video Imaging System (see page 192, col.1, paragraph 2). Metamorph is the preferred imaging system cited in the instant specification (see for example, paragraph [0096]). While Franciosi taught observing parameters such as cell proliferation and density rather than heart rate, Serbedzija taught use of automated computer software and measuring heart rate as a parameter of heart function. Franciosi taught determining pixel intensity (page 192, col, 1, paragraph 2) as a measurement tool.

Thus, while Serbedzija did not specifically teach each of the claimed method steps in using computer automation, Franciosi supports that these steps were well-known, if not inherent, in applying a computer based software program for screening, like Metamorph, to the claimed method of screening and measuring parameters of heart function such as heart rate. Thus, it would have been obvious at the time of filing to combine the teachings of Serbedzija regarding a high-throughput screening of the effects of compounds on heart rate, which uses computer software (col. 61, line 2-3), with the teachings of Franciosi in carrying use of the software by recording data and analysis of the heart with Metamorph software. One of skill in the art would have been motivated to make such a combination as Metamorph was a highly used and readily available imaging system for data analysis and was shown to work in imaging the heart by Franciosi. Furthermore, such automation allows for much more efficient, high-throughput screening.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

2) Claims 1-3,5,9-12,14,15,17-21,23-24,27-28,30-35,40,43-45,47,48,52-55,57 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Serbedzija (US 6,656,449, filed 09/23/2000) taken with Xiang *et al* (July 2002, JBC, 62:189-194).

Serbedzija taught a method of evaluating a test agent comprising method steps of contacting a zebrafish with a test agent, and evaluating a parameter of heart function (claim 1). Serbedzija taught screening compounds from the NCI Open Synthetic Compound Collection library (col. 23, lines 7-14) by administering the compounds in 6-96 well assay array plates to wildtype zebrafish embryos (col. 23, lines 35-40). Parameters to be evaluated included heart rate (col. 23, lines 54-55). Serbedzija teaches that the test compound can be a small molecule, nucleic acid or a protein (col. 14, lines 19-43) and that combinatorial libraries of compounds can be used. Serbedzija teaches screening multiple compounds in parallel using a multi-well plate. Serbedizija also taught that larval stages can be used in the method (col.

12, lines 46-47). Serbedzija also teaches permeabilizing the zebrafish by administering the agents in a DMSO solution (col. 20, lines 53-58).

Serbedzija also taught computer-based screening automation as claimed, Serbedzija did not teach recording the heart and analyzing the recording.

However, Xiang taught image recording of the contraction rate of cardiomocytes using a Metamorph Video Imaging System comprising video recording the cells through a video camera connected to a microscope and a computer that used MetaMorph software. The images were analyzed with MetaMorph and data was plotted using Microsoft Excel (see page 34281, col.1, paragraph 4). Metamorph is the preferred imaging system cited in the instant specification (see for example, paragraph [0096]).

Thus, while Serbedzija did not specifically teach each of the claimed method steps in using computer automation, Xiang supports that these steps were well-known, if not inherent, in applying a software program like Metamorph to the claimed method of screening and measuring parameters of heart function such as heart rate. Thus, it would have been obvious at the time of filing to combine the teachings of Serbedzija regarding a high-throughput screening of the effects of compounds on heart rate, which uses computer software (col. 61, line 2-3), with the teachings of Xiang in carrying use of the software by recording data and analysis of the heart with Metamorph software. One of skill in the art would have been motivated to make such a combination as Metamorph was a highly used and readily available imaging system for data analysis and was shown to work in imaging the heart by Xiang. Furthermore, such automation allows for much more efficient, high-throughput screening

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

3) Claims 1-3,5,8-9,11-12,14,15,17-21,22-24,27,30-36,40,43-45,47,48,52-55,57 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Artemis pharmaceuticals Inc., (WO 01/92874, filed 05/19/2001, published 12/06/2001), hereafter referred to as '874 taken with Franciosi *et al* (2000, Teratology, 62:189-194).

'874 teaches use of zebrafish embryos and larvae (page 3, lines 25-27; page 4, line 20) to screen agents for those that affect cardiac function in zebrafish (paragraph 0050 and 0060) using a 24 well array format (p.4, line 33). Parameters to be evaluated included heart rate, rhythm, contractility (p. 4 lines 15-18), which are measured in vivo in the intact fish. '874 teaches correlating effects found in zebrafish to effects on humans in teaching that various medications used in humans that have cardiac-related side effects has similar effect in zebrafish and thus the fish is an excellent test system for the side-effects of other potential drugs in humans (page 5, line 20-page 6, line 18). '874 teaches use of a number of small molecule drugs. '874 teaches treatment with multiple agents, including a second test agent (page 6, lines 20- page 7, line 7).

'874 did not teach recording the heart and analyzing the recording.

However, Franciosi taught image recording of the heart of chick embryos using a microscope coupled to a Metamorph Video Imaging System (see page 192, col.1, paragraph 2). Metamorph is the preferred imaging system cited in the instant specification (see for example, paragraph [0096]). While Franciosi taught observing parameters such as cell proliferation and density rather than heart rate, Serbedzija taught use of automated computer software and measuring heart rate as a parameter of heart function. Franciosi taught determining pixel intensity (page 192, col, 1, paragraph 2).

Thus, while '874 did not specifically teach each of the claimed method steps in using computer automation, Franciosi supports that these steps were well-known, if not inherent, in applying a software program like Metamorph to the claimed method of screening and measuring parameters of heart function such as heart rate. Thus, it would have been obvious at the time of filing to combine the teachings of '874

using zebrafish to screen for the effects of agents on parameters of heart function, with the teachings of Franciosi in carrying use of the software by recording data and analysis of the heart with Metamorph software. One of skill in the art would have been motivated to make such a combination as Metamorph was a highly used and readily available imaging system for data analysis and was shown to work in imaging the heart by Franciosi. Furthermore, such automation allows for much more efficient, high-throughput screening.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

4) Claims 1-3,5,8-9,11-12,14,15,17-21,22-24,27,30-35,40,43-45,47,48,52-55,57 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Artemis pharmaceuticals Inc., (WO 01/92874, filed 05/19/2001, published 12/06/2001), hereafter referred to as '874 taken with Xiang *et al* (July 2002, JBC, 62:189-194).

'874 teaches use of zebrafish embryos and larvae (page 3, lines 25-27; page 4, line 20) to screen agents for those that affect cardiac function in zebrafish (paragraph 0050 and 0060) using a 24 well array format (p.4, line 33). Parameters to be evaluated included heart rate, rhythm, contractility (p. 4 lines 15-18), which are measured in vivo in the intact fish. '874 teaches correlating effects found in zebrafish to effects on humans in teaching that various medications used in humans that have cardiac-related side effects has similar effect in zebrafish and thus the fish is an excellent test system for the side-effects of other potential drugs in humans (page 5, line 20-page 6, line 18). '874 teaches use of a number of small molecule drugs. '874 teaches treatment with multiple agents, including a second test agent (page 6, lines 20- page 7, line 7).

'874 did not teach recording the heart and analyzing the recording.

However, Xiang taught image recording of the contraction rate of cardiomocytes using a Metamorph Video Imaging System comprising video recording the cells through a video camera connected to a microscope and a computer that used MetaMorph software. The images were analyzed with MetaMorph and data was plotted using Microsoft Excel (see page 34281, col.1, paragraph 4). Metamorph is the preferred imaging system cited in the instant specification (see for example, paragraph [0096]).

Thus, while '874 did not specifically teach each of the claimed method steps in using computer automation, Xiang supports that these steps were well-known, if not inherent, in applying a software program like Metamorph to the claimed method of screening and measuring parameters of heart function such as heart rate. Thus, it would have been obvious at the time of filing to combine the teachings of '874 using zebrafish to screen for the effects of agents on parameters of heart function, with the teachings of Xiang in carrying use of the software by recording data and analysis of the heart with Metamorph software. One of skill in the art would have been motivated to make such a combination as Metamorph was a highly used and readily available imaging system for data analysis and was shown to work in imaging the heart by Xiang. Furthermore, such automation allows for much more efficient, high-throughput screening

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

5) Claim 83 is rejected under 35 U.S.C. 103(a) as being unpatentable over Serbedzija (US 6,656,449, filed 09/23/2000) in view of Asano (1997, **ACCC**, 29:831-842).

Serbedzija taught a method of evaluating a test agent comprising method steps of contacting a zebrafish with a test agent, and evaluating a parameter of heart function (claim 1). Serbedzija taught screening compounds from the NCI Open Synthetic Compound Collection library (col. 23, lines 7-14) by

administering the compounds in 6-96 well assay array plates to wildtype zebrafish embryos (col. 23, lines 35-40). Parameters to be evaluated included heart rate (col. 23, lines 54-55). Serbedzija teaches that the test compound can be a small molecule, nucleic acid or a protein (col. 14, lines 19-43) and that combinatorial libraries of compounds can be used. Serbedzija teaches screening multiple compounds in parallel using a multi-well plate. Serbedizija also taught that larval stages can be used in the method (col. 12, lines 46-47). Serbedzija also teaches permeabilizing the zebrafish by administering the agents in a DMSO solution (col. 20, lines 53-58).

Serbedzija did not teach measuring QT interval using voltage sensitive dyes as a parameter of heart function.

However, Asano taught the use of voltage sensitive dyes to measure QT interval for high resolution video imaging of electrical waves on the heart in conjunction with ECG. Asano teaches the relevance of QT interval to human disease such as long QT synndrome.

One of skill in the art would have been motivated to perform the screenfor agents affecting parameters of heart function taught by Serbedzija wherein the parameter is QT interval as taught by Asano as the QT interval was well known to be a parameter affected in human disease as demonstrated by Asano (paragraph 1 of the introduction, page 840, col. 2, paragraph 2). One of skill in the art would be motivated to screen for agents that affect QT interval because such agents would be candidates to treat heart disease, such as long QT syndrome, in humans and other mammals. One of skill in the art would have a reasonable expectation of success in carrying out the combination of teachings as the fish has the same functional parameters as mammals, including a QT interval.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

6) Claim 83 is rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson et al. [PNAS, 97:12965-12969, 2000] in view of Asano (1997, ACCC, 29:831-842).

Peterson et al taught use of zebrafish as a model to screen small molecules for various phenotypic effects on the cardiovascular system (page 12965, col. 2, paragraph 3). Peterson et al taught placing embryos in 96 well arrayed plate and adding small molecules from the DiverSet E library (page 1296, col. 2, paragraph 2). Peterson et al. taught administering the agent in a DMSO solution (p. 12965, col. 2, paragraph 2), which permeabilizes the zebrafish (see Serbedzija, US 6,656,449 at col. 20, lines 53-58).

Parameters of heart function were observed as Peterson et al. teach that 32P6 causes two edematous pericardial sacs to form, mimicking cardia bifida (page 12966, col. 1, paragraph 2). 31J6 affected heart contractility (page 12968). 31J6 causes an increase in the ratio of atrium to ventricle contractions. Peterson remarks that this particular small molecule causes effects correlating to second-degree atrioventricular heart block observed in humans, which is correlating the effect of the agent in the zebrafish with a predicted effect on heart function in humans. Thus, Peterson et al. administered small molecules to fish. Peterson evaluated parameters of heart function including structural development and contractility.

Peterson did not teach measuring QT interval using voltage sensitive dyes as a parameter of heart function.

However, Asano taught the use of voltage sensitive dyes to measure QT interval for high resolution video imaging of electrical waves on the heart in conjunction with ECG. Asano teaches the relevance of QT interval to human disease such as long QT synndrome.

One of skill in the art would have been motivated to perform the screen for agents affecting parameters of heart function taught by Peterson wherein the parameter is QT interval as taught by Asano as the QT interval was well known to be a parameter affected in human disease as demonstrated by Asano (paragraph 1 of the introduction, page 840, col. 2, paragraph 2). One of skill in the art would be motivated

to screen for agents that affect QT interval because such agents would be candidates to treat heart disease, such as long QT syndrome, in humans and other mammals. One of skill in the art would have a reasonable expectation of success in carrying out the combination of teachings as the fish has the same functional parameters as mammals, including a QT interval.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

7) Claim 83 is rejected under 35 U.S.C. 103(a) as being unpatentable overArtemis pharmaceuticals Inc., (WO 01/92874, filed 05/19/2001, published 12/06/2001), hereafter referred to as '874.

'874 teaches use of zebrafish embryos and larvae (page 3, lines 25-27; page 4, line 20) to screen agents for those that affect cardiac function in zebrafish (paragraph 0050 and 0060) using a 24 well array format (p.4, line 33). Parameters to be evaluated included heart rate, rhythm, contractility (p. 4 lines 15-18), which are measured in vivo in the intact fish. '874 teaches correlating effects found in zebrafish to effects on humans in teaching that various medications used in humans that have cardiac-related side effects has similar effect in zebrafish and thus the fish is an excellent test system for the side-effects of other potential drugs in humans (page 5, line 20-page 6, line 18). '874 teaches use of a number of small molecule drugs. '874 teaches treatment with multiple agents, including a second test agent (page 6, lines 20- page 7, line 7).

'874 did not teach measuring QT interval using voltage sensitive dyes as a parameter of heart function.

However, Asano taught the use of voltage sensitive dyes to measure QT interval for high resolution video imaging of electrical waves on the heart in conjunction with ECG. Asano teaches the relevance of QT interval to human disease such as long QT synndrome.

One of skill in the art would have been motivated to perform the screen for agents affecting a parameter of heart function taught by '874 wherein the parameter is QT interval as taught by Asano as the QT interval was well known to be a parameter affected in human disease as demonstrated by Asano (paragraph 1 of the introduction, page 840, col. 2, paragraph 2). One of skill in the art would be motivated to screen for agents that affect QT interval because such agents would be candidates to treat heart disease, such as long QT syndrome, in humans and other mammals. One of skill in the art would have a reasonable expectation of success in carrying out the combination of teachings as the fish has the same functional parameters as mammals, including a QT interval.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

8) Claim 83 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zon (**US2005/0155087**; EFD 12/17/2001).

Zon teaches use of zebrafish to screen the DIVERSet E library (paragraph 0161), for agents that affect cardiac function in zebrafish embryos and larvae (paragraph 0050 and 0060) using a 48 well array format (paragraph 0161). Zon teaches administering the agent in the culture media (paragraph [0012]) or by injection (paragraph [0014]). Parameters to be evaluated included heart rate (paragraph [0060] and wall motion (contractility), which are measured in vivo in the intact fish. Zon teaches correlating effects found in zebrafish to predicted effects on other mammals in teaching that compound have capacity to improve cardiac function have potential for treating cardiac failure in adults (humans). Zon teaches that the test compound can be a small molecule or a nucleic acid (paragraph 0067) or a hormone and that combinatorial libraries of compounds can be used (paragraph 0067-0068). Zon also taught that larval stages can be used in the method (paragraph 0010). Zon teaches screening multiple compounds in parallel using a multi-well plate. Zon taught administering the agent in a DMSO solution (paragraph 0071). Zon

taught administering a dye (paragraph [0071]) and detecting toxicity of the compound (paragraph [0070] and [0166]).

Zon does not teach measuring QT interval using voltage sensitive dyes as a parameter of heart function.

However, Asano taught the use of voltage sensitive dyes to measure QT interval for high resolution video imaging of electrical waves on the heart in conjunction with ECG. Asano teaches the relevance of QT interval to human disease such as long QT syndrome.

One of skill in the art would have been motivated to perform the screen for agents affecting a parameter of heart function taught by Zon wherein the parameter is QT interval as taught by Asano as the QT interval was well known to be a parameter affected in human disease as demonstrated by Asano (paragraph 1 of the introduction, page 840, col. 2, paragraph 2). One of skill in the art would be motivated to screen for agents that affect QT interval because such agents would be candidates to treat heart disease, such as long QT syndrome, in humans and other mammals. One of skill in the art would have a reasonable expectation of success in carrying out the combination of teachings as the fish has the same functional parameters as mammals, including a QT interval.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

The provisional rejection of claims 1,11,12,17-19,40 under 35 U.S.C. 101 as claiming the same invention as that of claims 1,2,9,10 and 15-17 and 19 of copending Application No. 11/149,662 is withdrawn in light of Applicant's amendments to the claims of both applications such that they are no longer obvious one over the other.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio, Ph.D./
Primary Examiner
Art Unit 1632